REMARKS

Claims 1 and 4-13 are pending in the application.

As a preliminary matter, Applicants note that the Examiner did not address claims 12 and 13 presented in the Amendment filed December 11, 2007.

I. Response to Claim Rejections under 35 U.S.C. § 103 - Obviousness

A. Rejection of Claims 1, 3-11 based on Scheiwe et al in view of Iyer et al

Claims 1 and 4-11 are rejected under 35 U.S.C. § 103 as being unpatentable over Scheiwe et al (U.S. 6,492,395) in view of Iyer et al (U. S. 2004/0033257). Specifically, the Examiner states that claims 3-4 and 9-11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Scheiwe et al and the rejection is maintained in regards to claims 4 and 9-11 and further applied to claims 1 and 5-8.

Applicant respectfully traverses the rejection and submit that the Examiner has not made a *prima facie* showing of obviousness.

The present invention is directed to a liquid pharmaceutical composition comprising pirfenidone or a pharmaceutically acceptable salt thereof in a concentration of 10% to about 25% by weight, and diethylene glycol monoethyl ether (DGME). The present invention is characterized in that a high concentration of the drug, pirfenidone, is used and formulation can be obtained which is stable. Additionally the composition of the present invention is stable even at low temperatures. Further, a true solution if the drug is obtained where there is no crystallization or phase separation.

Scheiwe et al teaches topical compositions such as creams ointments and gels comprising pirfenidone, but does not describe a composition comprising 10 to about 25% pirfenidone and

DGME. Specifically, Scheiwe et al describes a formulation preferably containing 3 to 7% pirfenidone in a topical gel dosage form for dermatological applications to the skin. The formulation of Scheiwe et al contains propylene glycol as a solvent for the drug. Compared to the present invention, the formulation of Scheiwe et al has a lower maximum concentration of 7% and is unstable at low temperatures. Also, the formulations of Scheiwe et al are not true solutions, but are super-saturations of the drug and with time, crystallization at low temperatures occurs.

The advantageous effects of the present invention in terms of stability are supported by the attached Declaration under 37 C.F.R. § 1.132.

As noted by the Examiner, Scheiwe et al describes a hydrophilic ointment composition comprising pirfenidone in an amount of 10% (wt/wt) in Comparative Example 1 at column 4. However, Scheiwe et al does not disclose a liquid composition comprising pirfenidone in an amount of 10 to 25% and DGME as recited in the present claims. As previously noted by Applicant, hydrophilic ointment is not a liquid based on its formulation (see for example, Scheiwe et al at paragraph [0081] and Remington's Pharmaceutical Sciences, 17th Ed., page 1304, previously submitted by Applicants). Hydrophilic ointments are "semisolids" and are not liquids.

Even further, Scheiwe et al teaches away from a composition comprising pirfenidone in an amount of 10% with standard exicpients in teaching that the preferred concentration of pirfenidone is 3 to 7% and in teaching a comparative example wherein pirfenidone is employed in an amount of 10% wt/wt and found to be unsuitable. Specifically, Scheiwe et al teaches that standard excipient preparations are unsuitable for use in the preparation of pharmaceutically acceptable topical formulations such as ointments containing a sufficient dosage of the active

ingredient because pirfenidone tends to physically destabilize emulsions and other colloidal systems. Column 1, lines 59-67. Scheiwe et al further teaches that the ointment preparations of Comparative Example 1 developed phase separation effects, the emulsion became inhomogeneous by coalescence effects and also large crystals developed upon storage. Thus, based on the teachings of Scheiwe et al taken as a whole, one of ordinary skill in the art would not have expected to achieve a suitable stable liquid formulation comprising 10 to 25% pirfenidone.

The Examiner states that Iyer et al is relied upon for the disclosure of solvents that dissolve poorly soluble compounds. However, there is no reason to combine Scheiwe et al and Iyer et al.

Iyer et al does not disclose, teach or suggest a liquid composition comprising pirfenidone, much less 10 to 25% pirfenidone and DGME and Iyer et al does not recognize the problems associated with making pirfenidone formulations at higher concentrations. Iyer et al teaches gelatin capsules comprising loratidine. Iyer et al specifically describes a formulation of loratidine, solubilized in a mixture of solvent and emulsifiers and which is specifically to be used in making soft gelatin capsules of this particular drug. The maximum concentration of the drug (as shown in Table 1 at paragraph [0030]) reached in the solvent mixture is 8% drug. Transcutol P alone is only one component along with a mixture of other components of the formulation (for making soft gelatin capsules of loratidine). Iyer et al teaches a different dosage form of a different drug in a lower concentration and is not a true solution, but a suspension in a solvent system, which is not at all relevant to the present invention. Further, Iyer et al can not be applied to all kinds of drug molecules, which are poorly water soluble. Thus, one of ordinary skill in the art would not have been motivated to modify the working examples of Scheiwe et al based on

the teachings of Iyer et al with a reasonable expectation of success in achieving a liquid composition comprising pirfenidone in a concentration of 10 to 25% as in the present claims. Hence, Iyer et al does not teach or suggest the presently claimed invention and does not remedy the deficiencies of Scheiwe et al.

Additionally, there is no apparent reason to combine Scheiwe et al and Iyer et al. Specifically, Scheiwe et al teaches topical compositions comprising pyridone derivatives, more specifically pirfenidone, whereas Iyer et al teaches gelatin capsules comprising loratidine. Loratidine is not a pyridone derivative and Applicant has pointed out that there are significant structural differences between loratidine and pirfenidone, such that one of ordinary skill in the art would not consider the compounds to possess similar solubility and stability characteristics. Therefore, there is no apparent reason for one of ordinary skill in the art to expect a solvent suitable for loratidine to be suitable for pirfenidone.

The Examiner admits that Iyer et al does not specifically disclose pirfenidone as a drug that could be dissolved in the solvents described therein, but the Examiner asserts that "it would have been in the relative skill in the art to look to the prior art to identify solvents useful in dissolving poorly water soluble compounds for pharmaceutical use". However, Applicant submits that the Examiner's conclusion is legally improper as it has been held that it is insufficient to establish *prima facie* obviousness based on the assertion that a modification is within the capabilities of one of ordinary skill in the art without an objective reason to make the modification. See MPEP § 2143.01. Considering the differences between the formulations (i.e., topical formulations vs. gelatin capsules for oral administration) and active ingredients (i.e., pyridone derivatives, such as pirfenidone vs. loratidine) taught by Scheiwe et al and Iyer et al,

one of ordinary skill in the art would not have been motivated to combine the references as suggested by the Examiner.

As the active ingredients in Scheiwe et al and Iyer et al are unrelated and the formulations are unrelated, the Examiner seems to suggest that it would have been obvious for one of ordinary skill in the art to consider any solvent known to be useful for dissolving any poorly water soluble compound which is analagous to an "obvious to try "argument. However, the number of poorly water soluble compounds and the number of potential solvents to choose from may not be considered a finite number of possible solutions as required to sustain such a rejection. Indeed millions of dollars are spent by pharmaceutical companies every year to develop new formulations of "poorly soluble drugs" and several different factors are taken into account such as route of administration, solid state solubility, solution solubility, aqueous solubility at a range of pH's, hygroscopicity, crystallinity, salt selection, absorption, bioavailability and physical properties of the drug molecule, etc., as evidenced by the attached article, "Taking Poorly Water Soluble Compounds Through Discovery". Iyer et al does not teach that Transcutol P is a suitable solvent for all poorly soluble drugs and therefore it is not reasonable to assert that based on the teachings of Iyer et al that Transcutol P is a suitable solvent for loratidine, one of ordinary skill in the art would automatically expect Transcutol P to be a suitable solvent for pirfenidone taught by Scheiwe et al simply because pirfenidone is also a poorly soluble drug. The bottom line is that there is no apparent reason to choose DGME as a solvent to be used in combination with pirfenidone or to choose pirfenidone as the poorly water soluble compound in combination with DGME based on the teachings of Scheiwe et al and Iyer et al.

Applicant respectfully submits that the Examiner has engaged in improper hindsight reasoning as there is no apparent reason for combining the references.

Accordingly, the present invention is not rendered obvious over the cited references and Applicant respectfully requests withdrawal of the rejection.

B. Rejection of Claims 1, 4 and 8 based on Margolin in view of Iyer et al

Claims 1, 4 and 8 are rejected under 35 U.S.C. § 103 as being unpatentable over Margolin (WO 94/26249) in view of Iyer et al (U.S. 2004/0033257). Specifically, the Examiner states that claims 3-4 were rejected under 35 U.S.C. § 103 as being unpatentable over Margolin in view of Iyer et al and the rejection is maintained as to claims 3-4 and is further applied to claims 1 and 8. The Examiner's characterization and analysis are set forth on pages 4-7 of the Action.

In response to the Applicant's arguments that Margolin is not enabling, the Examiner states that the reference does not have to provide examples of how to make each dosage form in order to be enabling. According to the Examiner, Margolin discloses the amount of pirfenidone to be 1% to 20%, therefore teaching and suggesting a liquid composition comprising pirfenidone in a range from 10% to 25%. The Examiner states that it would also have been in the relative skill of one of ordinary skill in the art to look to prior art such as Iyer et al to determine which solvent would be suitable to make the recited liquid dosage forms Iyer et al, especially in view of the disclosure by Iyer et al which discloses "Transcutol P is purified diethylene glycol monoethyl ether that acts as a powerful solubilizer for several poorly soluble drugs. It is soluble in water, ethanol, hexylene glycol and propylene glycol, and partially soluble in vegetable oils. It also acts as a co-surfactant in the formulation" (paragraph 0024). According to the Examiner, it would have been obvious to use it to make more concentrated pharmaceutical solutions of other poorly soluble drugs.

In regard to the Declaration, the Examiner states that Applicant has not provided objective evidence to support the assertions of the problems of solubilizing pirfenidone or other assertions made in the Declaration other than Remington's Pharmaceutical Sciences book. Although the examples disclosed do not provide a method of making the compositions, one of skill in the art would be able to look to resources such as Remington' Pharmaceutical Sciences book (as suggested by the Declaration when it was used by Applicant to show how hydrophilic creams are made) to make the disclosed dosages.

In regard to Example 2 of Margolin, the Examiner states that one would look to the art to determine suitable co-solvents in the event that the drug of choice, at the desired concentration, was poorly soluble in water, as in the case of pirfenidone. The Examiner further asserts that one would only need to find a suitable co-solvent to make compositions of higher concentrations.

Applicant respectfully traverses the rejection and submit that the Examiner has not made a *prima facie* showing of obviousness as there is no apparent reason to combine the references as suggested by the Examiner and because Margolin is not enabling.

Regarding the Examiner's position that Margolin does not have to provide examples of how to make each dosage form in order to be enabling, Applicant submits that the question is whether Margolin is enabling for a liquid composition comprising 10 to 25% pirfenidone as presently claimed. In order for a prior art reference to be enabling, the reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. Thus, Applicants submit that the mere naming of formulations of 1-20% concentration and the mere disclosure of hydrophilic ointment having an amount of pirfenidone of 10% (or more) without a description of how such is obtained and without recognizing the problems associated with making such an

ointment, much less a liquid as presently claimed, is not sufficiently enabling since there is no direction, guidance or specific example of such a product. In this regard, Applicant notes that Scheiwe et al discloses:

> . . . standard excipient preparations e.g. as described in the USP (United States Pharmacopoiea) are unsuitable for use in the preparation of pharmaceutically acceptable formulations such as ointments containing a sufficient dosage of the active ingredient. The preparations lack physical stability. It was found that 5-methyl-1-phenyl-2-(IH)-pyridone is a so called emulsion destabiliser, i.e. tends to destabilize physically emulsions and other colloid systems.

This disclosure of Scheiwe et al is objective evidence of the problems associated with making pirfenidone formulations and supports Applicant's position. The fact that Margolin does not describe the specific excipients and method of making the hydrophilic ointment mentioned therein indicates that it was made according to conventional techniques and Scheiwe et al clearly states that such preparations are not suitable for use in pharmaceutically acceptable formulations and lack physical stability. Scheiwe et al also provides examples of several compositions made using standard excipient preparations which were found to lack stability including hydrophilic ointment having 10% wt/wt pirfenidone. Thus, it can be inferred that the hydrophilic ointment of Margolin et al also lacks stability or that Margolin is otherwise nonenabling for how to make a stable hydrophilic ointment having a concentration of 10% since there is no description as to how the disclosed ointment is made. It therefore follows that Margolin is not enabling for making any other pharmaceutically acceptable composition comprising pirfenidone in a concentration of 10 to 25%, much less a liquid pharmaceutical composition comprising pirfenidone in a concentration of 10 to 25% in combination with DGME, since there is no recognition of the problems associated with making such a composition and no disclosure, example or guidance as to how such a composition could be obtained.

The Examiner states that it would have been within the relative skill in the art to look to the prior art such as Iyer et al to determine which solvents would have been suitable to make the recited liquid dosage forms. However, as stated above, the Examiner's conclusion is legally improper as it has been held that it is insufficient to establish *prima facie* obviousness based on the assertion that a modification is within the capabilities of one of ordinary skill in the art without an objective reason to make the modification. See MPEP § 2143.01. In this case neither of Margolin nor Iyer et al recognize the problems associated with making pirfenidone formulations and therefore there is no objective reason for one of ordinary skill in the art to modify or combine the references.

Even if Margolin et al could be considered as enabling (a point which Applicant does not concede), there is no apparent reason to combine Margolin et al and Iyer et al. Margolin et al only names a topical composition comprising pyridone derivatives, more specifically pirfenidone, whereas Iyer et al teaches gelatin capsules comprising loratidine. Loratidine is not a pyridone derivative and there are significant structural differences between loratidine and pirfenidone, such that one of ordinary skill in the art would not consider the compounds to possess similar solubility and stability characteristics. Therefore, there is no apparent reason for one of ordinary skill in the art to expect a solvent suitable for loratidine to be suitable for pirfenidone. As stated above, millions of dollars are spent by pharmaceutical companies every year to develop new formulations of "poorly soluble drugs" and several different factors are taken into account. Iyer et al does not teach that Transcutol P is a suitable solvent for all poorly soluble drugs and therefore it is not reasonable to assert that based on the teachings of Iyer et al that Transcutol P is a suitable solvent for loratidine, one of ordinary skill in the art would

automatically consider Transuctol P to be a suitable solvent for pirfenidone taught by Margolin et al simply because pirfenidone is also a poorly water soluble drug.

Also, Margolin names a hydrophilic ointment which is not a liquid. Therefore, the present invention would not have been achieved even if the references were combined.

Additionally, Applicant submits that the Examiner engages in improper hindsight reasoning as there is no apparent reason for combining the references and choosing DGME as a solvent for pirfenidone or choosing DGME as the solvent for pirfenidone for the reasons set forth above. Although Iyer et al discloses that DGME acts as a powerful solubilizer for several poorly soluble drugs, Iyer et al does not disclose, teach or suggest pirfenidone as a poorly water soluble drug for which DGME is useful. Iyer et al also does not disclose that DGME is a solvent for all poorly water soluble drugs and therefore there is no apparent reason for one of ordinary skill in the art to expect that DGME would be a suitable solvent for pirfenidone.

Specifically, regarding the Examiner's position that one of ordinary skill in the art would only need to find a suitable co-solvent to make the compositions of Margolin in higher concentrations, Applicant submits that there is no motivation to specifically select DGME as such a solvent. Further, neither Margolin nor Iyer et al recognizes the problems associated with making a liquid composition using high concentrations of pirfenidone and it is only with improper hindsight reasoning that the Examiner arrives at a conclusion of obviousness in suggesting that one would only have to find a suitable co-solvent.

In view of the above, Applicant submits that the present invention is not rendered obvious by the combination of Margolin and Iyer et al and withdrawal of the rejection is respectfully requested.

II. Claims 12 and 13

Claims 12 and 13 were not addressed by the Examiner.

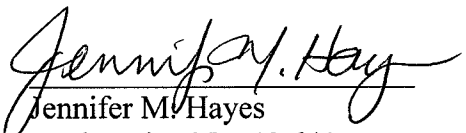
Applicant respectfully submits that claims 12 and 13 each depend from claim 1 and are patentable for at least the same reasons. Additionally, Applicant notes that the present invention provide unexpected advantages due to the combination of pirfenidone and DGME including good stability, lack of skin irritation and clinical safety.

III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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Date: July 28, 2008

Journées Galéniques, 1999

TAKING POORLY WATER SOLUBLE COMPOUNDS THROUGH DISCOVERY

David A. WYATT
Glaxo Wellcome R & D Ltd, Ware, Hertfordshire, UK

Appl. No. 10/540,422
Docket No. Q88273
Amdt. Dated July 28, 2008
Reply to Office action of April 30, 2008
Attachment

1. INTRODUCTION

The business of drug discovery is one in which the contribution of each scientific discipline is critical in the identification, optimisation, selection and onward development of the molecule to the marketplace. Inadequate contributions from any of the partners in medicine development can lead to very significant difficulties later in the process. Compounds with less than ideal properties can create difficulties in primary and secondary manufacturing, in clinical research, in regulatory and at almost any stage in the development process. At a time when the cost of developing medicines continues to escalate, and is certainly greater than US $300 million per molecule, any delay could be the difference between having an effective life saving medicine on the market, at the earliest possible opportunity, and, in the severest case, having a product that is financially non-viability. It is therefore of critical importance that as much work as can be accommodated is executed at the earliest phase of product development where costs are lowest, the stage that has become known as 'Discovery'.

To the formulation scientist 'preformulation' is the stage of development during which the physico-chemical properties of a drug substance are characterised and is the first opportunity for the pharmaceutical discipline to make a major contribution to the drug discovery process. Some commonly evaluated parameters include solubility, stability, partitioning, dissolution behaviour and solid state properties and these form the basis of the 'developability' assessment on any molecule. A complete understanding of for the development of a robust formulation with optimal performance in both *in vitro* and *in vivo* studies. Increasingly, computer modelling and simulation (designated '*in silico*') techniques are being utilised as selection tools in the search for molecules that will possess the best pharmaceutical properties.

Detailed reviews of pharmaceutical preformulation have been published (1) so it is not the purpose of this paper to cover this material in any detail. Rather it is its purpose to look more specifically at the considerations and tools available to the formulator who has the challenge of taking poorly water soluble compounds through the earliest phase of development. By 'poorly soluble' it is intended to include compounds that have limited solubility in water (typically < 0.1 mg/mL) and also often have low solubility in common pharmaceutical solvents. Although all the general principles of preformulation apply to these compounds, there are certain preformulation aspects that are unique. These aspects need to be considered to ensure the successful development of formulations for these agents. The goal of this paper is to discuss some theoretical and practical considerations for the preformulation of insoluble compounds with particular reference to their progression through the earliest phases of drug development.

2. THE DISCOVERY PHASE OF MEDICINE DEVELOPMENT

The discovery phase of drug development

- Lead Identificat
- Lead Optimisation
- Pre-Clinical Evaluation
- Clinical Concept Testing (sometimes called Proof of Concept).

As a molecule progresses through these phases, the characteristics of the New Chemical Entities (NCE) must become so well defined that the organisation gains high confidence that it will be able to meet the projected product profile. Each discovery project starts with a scientific rationale and a biological target but must very rapidly progress to having a viable product profile and a commercial justification. Combinatorial Chemistry and modern screening techniques mean that potentially many molecules can be identified that could meet the product profile, so potency and selectivity at a particular biological target are no longer the sole parameters upon which drugs candidates are selected. Many pharmaceutical companies are now developing new screens to differentiate molecular templates on a much fuller range of characteristics as part of the lead selection process (Table I).

Table I: Screening characteristics for Drug Candidates.

Potency
Selectivity
Physiochemical Properties
Kinetics
Tissue penetration
Carcinogenicity

High on this list of screens are a number measuring physicochemical parameters with high throughput at over a hundred compounds per day. Such screens range from computer models, trained on well characterised molecules and then predicting theoretical values from chemical structures to those that have been developed to automatically screen libraries of compounds at micromolar to millimolar concentration.

Once a can ' 'ate molecule has been selected, progression through the discovery stages is driven by the confidence of the organisation and this must be grown, except when the molecule has a clinically validated mechanism of action, in a less than ideal environment. In pharmaceutical development terms, this means with very little drug substance. Typically, the discovery phase will be conducted when the scale of synthesis is moving from 100 milligram per batch to 10g per batch and the chemistry responsibility is being transferred from the Research Chemist to the Development Chemist. Final drug form may still be undefined and final routes of manufacture may be even more remote. The bulk of the drug substance available is committed to safety evaluation studies and quantities of as little as 100mg are begrudgingly spared for pharmaceutical evaluation. On top of this, many of the candidate molecules, with high potency and selectivity, have poor solubility.

With these limitations, the formulation scientist needs to adopt a number of strategies to make a positive contribution to the discovery team. Firstly, the formulation scientist must draw on the experience of taking molecules all the way to the marketplace and assist the team in identifying those key properties that are required for the molecule to be delivered by various routes of administration. Although the oral route is favoured for most medicines there are potential biopharmaceutical advantages for intranasal, intravenous and inhaled delivery, for example rate of onset. It is also possible to validate the scientific concept without developing the final dosage form. The pharmaceutical scientist can also provide specific measurement expertise in analysis of the pharmaceutical properties. The miserly 100mg can yield a battery of data on, accelerated solid state stability, solution stability, aqueous solubility at a range of pH's, hygroscopicity and crystallinity that enable molecules to be differentiated on the basis of how simple or difficult they might be to develop ("developability"). In addition, where

molecules with less than ideal physical form have been selected, salt selection and crystallinity screened are utilised. Most importantly, the formulator can advise on appropriate formulations for pharmacokinetic, metabolism and pre-clinical safety studies to optimise the potential for absorption and exposure of the molecule, all of which will assist in the development of formulations for man.

In each of these activities, the formulation scientist must strive to understand the underlying mechanism of drug absorption so that the most appropriate formulation is developed.

3. EXTENT OF DRUG ABSORPTION

The ability to accurately predict the extent to which any molecule will be absorbed after oral administration would be an invaluable tool in drug development. This would enable the scientist to pre-select the chemical space in which to work and ensure that all the formulations to be taken to the marketplace would be simple and easy to develop. Although the vast majority of medicines are delivered via the oral route, the uptake of drug via this route can be highly erratic and inefficient. This is because the gastrointestinal tract is of immense complexity, with a wide range of pH levels, enzyme activity, and bacterial flora, that provides not just one but a range of environments that may be deleterious for the drug. The modelling of any one of these environments is a significant challenge but there are in the literature a number models that will help the formulator to gain *in silico* insight into the *in vivo* processes that affect the absolute bioavailability of the drug candidate.

In order to be absorbed, drugs must be hydrophilic enough to be solubilised (solubility), yet lipophilic enough to get across the gastrointestinal membrane (permeability). These two factors are the basis of the Biopharmaceutics Classification System(2) and, if they can be elucidated and understood, are the most efficient route to the development of new products.

3.1 Fundamental Factors Affecting Oral Drug Absorption

The primary variables that influence oral drug absorption and, hence, govern the efficacy of drug therapy can be divided into three categories: physiological factors, physicochemical factors, and dosage form factors. Although only the latter two are the primary concern of the formulation scientist, and this paper, it is nevertheless important to at least have a qualitative handle on the first.

3.1.1 Physiological factors

The absorption of a drug substance, delivered orally, will be highly dependant upon a wide range of physiological factors associated with the absorptive site(s) in the gastrointestinal (GI) tract (Table II), e.g. GI pH, gastric emptying rate, intestinal motility, blood flow, GI mucin and bile, and co-ingested food.

3.1.2 Physicochemical factors

A large amount of attention is rightly given to drug solubility but there are a number of other physicochemical factors that can radically effect absorption. These include lipophilicity, ionisation and chemical stability in the GI tract. A simple measurement of the aqueous solubility of a substance is not necessarily a good pointer to its bioavailability as the true solubility of a drug in vivo may be significantly different.

Factors influencing solubility include:

- the physical form of the drug substance (e.g. intrinsic polymorphism, crystallinity)
- salt formation (and the form of the salt)
- concentration of native surface active agents (such as bile salts)
- influence of co-ingested foods, particularly fatty foods (these in turn can affect the GI pH and assist dissolution through solubilisation / complexation).
- potential of the drug to ionise (pKa)

pKa and pH will affect the solubility (C_s).

i.e. weak acid: $C_s = C_0 (1 + Ka / [H])$ -(1)

weak base: $C_s = C_0 (1 + [H] / Ka)$ -(2)

where C_0 is the intrinsic solubility and Ka is the dissociation constant.

Table II: Schematic Environments in the ...ract.

Site of Absorption	Physiological factors	Mechanism of Absorption	Type of Dosage Form deliverable
Mouth	pH 6.2 - 7.4; Limited volume; Taste	Passive. Only lipophilic compounds are absorbed due to short time contact.	Chewable formulations, fast dissolving, bioadhesive dosage forms.
Oesophagus	pH: 5 - 6 25 cm long; 2 cm diameter; short transit time.	No absorption capacity.	Adherence of drugs can cause local ulceration or delayed absorption.
Stomach	volume (empty) of approximately 50 mL; pH 1 - 3.5, up to 5 with food.	Gastric emptying: 10 - 20 minutes in fast status and 10 minutes - 2 hours or longer in fed status. Absorption capacity: low due to small surface area and short exposure time.	Drugs may be metabolised or degraded in the stomach.
Small Intestine	350 cm long, 2 - 4 cm in diameter; 125 mL - 1.1 liters in volume; pH 5 - 8, transit time: 199 + 78 minutes (SD)	Passive diffusion: most common mechanism; Carrier-mediated transport including facilitated diffusion and active absorption. Primary site of absorption (due to large surface area).	Enteric coating; Controlled release
Colon	includes caecum (8.5 cm long); ascending colon (20 cm long), transverse colon (70 cm long); pH: 6.4 - 8.0; transit time: approximately 35 hours	Avoidance of first-pass metabolism and decreased enzyme concentration when compared to the small intestine. Absorption capacity: medium to large (due to long exposure time).	Enteric Coating; Controlled release Site-specific delivery, especially, peptide and protein.

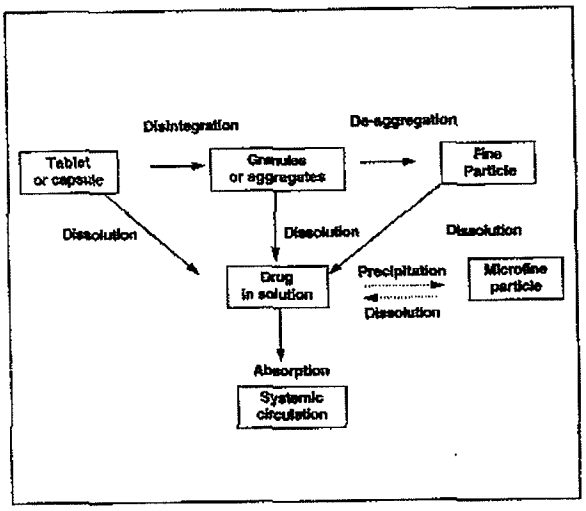
Other factors that can affect absorption are the physical properties of the molecule. For example a drug with a molecular weight of greater than 500 will not be readily absorbed in an intact form from the GI tract. Drugs with a high lipophilicity (logP > 5) are generally poorly absorbed through the GI tract and any molecule that is degraded at low pH will not have a significant bioavailability. Lipinski(3) has deduced a empirical 'Rule of 5', based on a simple assessment of physicochemical descriptors of the molecule, that enables the discovery scientist to rapidly screen any molecule for absorptivity and hence the likelihood of being a suitable drug candidate.

3.1.3 Dosage Form

Dosage form can have a significant influence the rate and extent of drug absorption. In principle, the formulation scientist can manipulate the drug substance through the modification of particle size or by creating amorphous particles or by solubilisation/

complexation to enhance or decrease its rate of dissolution (not its intrinsic solubility) and thereby present any molecule in the best possible form for absorption. Dosage forms include solution, suspension, capsule, tablet, coated tablet, and enteric-coated tablet and so the main influence of the dosage form is generally related to the dissolution (and precipitation) (Figure 1) of the drug substance in the GI tract. In discovery, the sophistication of the formulation for oral delivery is generally limited, by the scarcity of drug substance, to the use of aqueous (or non-aqueous) solutions or suspensions. The ability to extrapolate formulation science from these simple systems to more complex dosage forms is far from an exact science so, once again, prediction and modelling are often the only useful tools.

Fig 1: The drug absorption process (schematic).



3.2 Prediction of the Extent of Drug Absorption

Prediction of extent of oral drug absorption may be used to accelerate the screening of new molecular entities and the development of new products and a range of qualitative and quantitative tools exist.

3.2.1 Qualitative models

Qualitative tools are of high value to the formulation scientist because they can be utilised without use of large amounts of experimental work or computer time. However the relative non-sophistication of such models means that they can best be used as guide in selection. Such tools have their place in discovery until the quantitative tools have undergone a full *in silico - in vivo* validation.

3.2.1.1 pH-partition hypothesis(4)

On the assumption that absorption only occurs in the un-ionised form of the drug molecule, absorption is calculated from a knowledge of the proportion of the drug substance that is this state. The relationship between pKa and pH is:

for acids, $pH = pKa + \log (f_i/f_u)$ -(3)
for bases $pH = pKa + \log (f_u/f_i)$ -(4)

where f_u and f_i are the fractions of the drug in the unionised and ionised forms, respectively. This model has severe limitations when applied to poorly soluble drugs.

3.2.1.2 Absorption Potential

A more sophisticated model that may be more representative in the evaluation of poorly soluble drugs, has been developed by Dressman et al(5). This model incorporates drug solubility, partition coefficient, dose, and ionisation into a parameter known as the absorption potential. The absorption potential (AP) is calculated from the following equation:

$$AP = \log (P.C_S.V.\ f_u/M_O) \qquad -(5)$$

where P is the partition coefficient, C_S is the solubility at pH 7, V is the volume of water taken with drug (assume to be 250 mL), and M_O is the dose. An AP of greater than 1 suggests that the dose of drug would be completely absorbed.

3.2.2 Quantitative models

Yu et al (6) have published an excellent review of the estimation of the fraction of the dose absorbed so rather than review the quantitative models themselves, this paper will review some of the fundamental parameters required for determining the dose limiting factors. To the formulation scientist the major challenge is to understand what is limiting the absorption of the dose and then

to adopt formulation str ies to overcome these hurdles.

3.2.2.1 Fundamental parameters

As already discussed there are a number of physicochemical parameters, measured or predicted, that can give a guide to the absorption limiting factors. Solubility (C_s) can be measured under range of conditions; low pH, simulated fasted/fed state/gastric fluid but often aqueous solubility at pH 7 (pH of the lower GI tract) is utilised. Permeability (P_{eff}) measurements are analysed across a range of *in vitro* or *in vivo* media. Immortalised cell lines (e.g. Caco-2) or rat/dog data are proving to be useful surrogates for human permeability data. The product profile and the potency/selectivity data ought to give a good estimate of the intended human dose (M_0) although sometimes it is useful to use the upper limit on 'cost of goods' to define the maximum economic dose. For more mechanistic modelling molecular, diffusion is measured (Diffusion coefficient, D) or estimated. Particle size (r_0) and density (ρ) can have a significant bearing on absorption and are readily measured or modelled. Armed with this relatively small number of parameters it is possible to predict how drug candidates might perform.

3.3 Quantitative Estimation of Absorption/ Causes of Poor Absorption

Oral drug absorption can be simplistically considered as consecutive processes of dissolution and absorption (permeation) and even more simplistically, for a chemically stable drug, poor absorption can be thought to be caused by an inadequate rate of drug dissolution and/or low permeation. Low permeation could be caused by poor membrane permeability and/or by a low drug concentration (solubility) in the intestinal lumen. This means that oral drug absorption can be limited by drug dissolution rate, by membrane permeability, and/or by solubility.

A number of simple calculations can help the formulator to gain an insight into how solubility and rate of dissolution and or permeability might affect absorption.

3.3.1 Dose v me (V_{dose})

The minimum amount of water required to dissolve a dose of drug, the 'dose volume' can be calculated using the following equation.

$$V_{dose} = M_0/C_s \qquad -(6)$$

where M_0 is the dose and C_s is the solubility. If the calculated volume of water required to dissolve the dose is more than 250mL then the absorption is likely to be solubility limited.

3.3.2 Dissolution time

The theoretical time that is would take a drug particle to dissolve (T_{diss}) can be calculated from a range of physicochemical parameters

$$Tdiss = \rho.h.r_0/3\ D\ C_s \qquad -(7)$$

where ρ is the particle density, h is the thickness of the diffusion layer around the drug particle, r_0 is the radius of the drug particle, D is the diffusion coefficient, and C_s is the solubility. If T_{diss} is significantly longer than the residence time of the drug at the site of absorption then drug absorption will be dissolution rate limited. Since the rate of dissolution can be enhanced by particle size reduction, this calculation can be used to deduce the possible effect that micronising the drug substance might have on absorption (with the constraint of being able to produce monodisperse particles).

3.3.3 Absorbable Dose

The maximum amount of drug that can be absorbed, the absorbable dose (D_{abs}) can be calculated from some simple assumptions about the residence time of dissolved drug in the small intestine and a measure of permeability.

$$D_{abs} = P_{eff} . C_s . A . \langle T_{si} \rangle \qquad -(8)$$

where P_{eff} is the effective permeability, C_s is the solubility, A is the surface area of the small intestine (630 cm^2), and $\langle T_{si} \rangle$ is the mean small intestinal transit time (199 minutes). Ideally the permeability data would be derived from human studies but can be surrogate data from *in vitro* 'cells on sheets' or from animal studies.

Table III: Factors limiting Drug Absorption.

Absorption limiting factors	Physicochemical Constraints	Observations
Solubility Limited	T_{diss} is less than 20 minutes P_{eff} is greater than 2 x 10^{-4} cm/s	Dissolution is relatively fast. Permeability is fast. Solubility limited absorption often occurs because the gut is saturated by a high dose. Absorption does not increase with increased dose.
Dissolution limited	T_{diss} is greater than residence in small intestine P_{eff} is greater than 2 x 10^{-4} cm/s	Dissolution is slow and is therefore absorption limiting even though permeability is fast. Dissolution rate can be enhanced by particle size reduction. Absorption increases with increasing dose.
Permeability limited	T_{diss} is less than 50 minutes P_{eff} is less than 2 x 10^{-4} cm/s	Permeability low regardless of the solubility of the drug substance. The absolute amount of drug absorbed increases with increasing dose.

3.4 Summary of factors limiting absorption

Table III summarises the factors that can limit absorption of drug: dissolution, permeability and solubility. The discussion of permeability limited drug absorption is beyond the scope of this paper(7).

4. FORMULATION STRATEGIES FOR POORLY SOLUBLE COMPOUNDS

If the cause of poor absorption can be elucidated there are a number of formulation strategies that can be employed to optimise absorption. In the case of poorly soluble drugs most of the strategies are targeted at enhancing the dissolution rate and or solubility *in vivo*. For this purpose, *in vitro* dissolution studies are widely used to model the likely physical chemistry of dissolution(8).

4.1 Formulation of Solubility Limited Compounds

A true solution of drug is one in which the drug molecules are dispersed evenly throughout the solvent medium. The degree to which the molecules are dispersed and the degree to which the molecules are solvated will have a significant influence on how readily the molecules aggregate and precipitate on dilution and mixing *in vivo*. Hence a fundamental objective of formulating drugs with solubility limited absorption should be obtaining as highly dispersed a drug as possible. In the discovery phase this is probably best achieved by administering the drug in some kind of liquid form. Since by definition the drug substances of interest in this paper are poorly soluble in aqueous media, this could possibly be achieved by using an emulsion or micro-emulsion/self-emulsifying system or possibly by utilising lipids or pure oils. Bile salt can enhance the drug solubility *in vivo* up to 100-fold. Lecithin, mono-oleins, long chain fatty acids and/or triglycerides can further increase the solubility of the drug. Such liquid systems could be encapsulated in soft or hard gel

capsules that can be manufactured on a small scale. This type of formulation cannot guarantee that the drug will not precipitate and the mechanism of absorption from such systems is often poorly understood(8). Nevertheless such formulations have a place in the earliest phase of the evaluation of poorly soluble compounds because they can be utilised with small quantities of drug.

Another approach utilising a solid dosage form is to design a super-saturated system that holds the drug in solution for a maximum time frame prior to precipitation. This can be achieved by utilising solid dispersions or co-precipitates in which an inert excipient is formulated with the drug substance to hold the drug in an amorphous state. This ensures that the drug is held in one of its most soluble forms. Potentially this could also be achieved by selecting a suitable highly soluble polymorph or salt, but once again finding this form would be extremely fortuitous where a minimum of drug substance is available. It should be re-emphasised that in solubility limited absorption the absolute amount of drug absorbed does not increase with increasing dose.

4.2 Dissolution limited absorption

Many of the constraints associated with solubility limited absorption are common to those in dissolution limited absorption. Each of the above approaches (section 4.1) could be adopted to enhance the solubility of the drug substance. Theoretically the simplest way to enhance the rate of dissolution of a solid particle is to increase its radius of curvature, i.e. reduce its particle size. This can be achieved through the use of a range of particle reduction techniques from air-jet milling (micronisation) to microfluidisation or by creating nanoparticulate systems. These latter systems, created by spray or freeze-drying or by grinding are comprised of sub-micron particles that are amenable for direct use in intravenous formulations and therefore can be used for absolute bioavailability studies. These techniques are quite viable in the discovery phase of drug development but carry with them a technology burden if progressed to full development.

5. CONCLUSION

The discovery phase of drug development presents formulation scientists with significant challenges. Firstly they must bring their knowledge of the full development process to bear to influence the discovery team into lead areas with desirable pharmaceutical properties. Secondly, they must advise the team on those properties that are desirable for all routes of administration and thirdly they must play their part in the characterisation of lead compounds so as to optimise their developability. Where lead compounds have poor solubility, the formulation scientist must seek to understand the underlying mechanisms of absorption so as to adopt a formulation strategy that optimises the drug absorption. In order to do this, the scientist must use appropriate models and tools that as far as possible minimise drug usage but nevertheless allow the project team to select molecules that are likely to be developable to the marketplace. In this quest there is undoubtedly an important place for alternative formulation vehicles and in particular liquid vehicles that keep the drug dispersed and potentially available as it transits the GI tract.

ACKNOWLEDGEMENTS

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SUMMARY

TAKING POORLY WATER SOLUBLE COMPOUNDS THROUGH DISCOVERY

Preformulation may be described as a stage of development during which the physico-chemical properties of a drug substance are characterised. Some commonly evaluated parameters include solubility, stability, partitioning, dissolution behaviour and solid state properties including crystal forms/polymorphs, water sorption behaviours, surface properties, particle size, and particle shape. A complete understanding of these physicochemical properties is essential for the development of a robust formulation having optimal performance. Detailed reviews of pharmaceutical preformulation have been published (Fiese and Hagen, 1986, Wells, 1988, Ravin and Radebough, 1990). Compounds that have limited solubility (typically < 0.1-1 mg/mL depending on the potency of compounds) in water and in common pharmaceutical solvents present unusual challenges. Although all the general principles of preformulation apply, there are certain preformulation aspects that are unique to insoluble compounds. These aspects need to be considered to ensure the successful development of formulations for these agents.

The goal of this paper is to discuss the theoretical and practical considerations for the preformulation of insoluble compounds with particular reference to their progression through the earliest phases of drug development.

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